HPV vaccination: How long does the protection really last?

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Knowledge of duration of protection is essential for planning of vaccination programs – in case of waning immunity a booster vaccination may be required.

*Ethical/methodological issues make reliable assessment of long-term duration of protection difficult.

- No longer possible to compare with a randomised control group that did not get the vaccine: Most trials have vaccinated the placebo group.

*Absence of cases among vaccinated women is an indication that protection may be lasting.
Inference on duration is based on:

- RCT on monovalent HPV16 vaccine (Merck): 8.5 years
- RCT on bivalent vaccine (GSK): 9.4 years
- Long Term Follow-up of quadrivalent vaccine (Nordic): 8 years.
- Immunogenicity studies.
- Comparisons with the natural immunity.
RCT on monovalent HPV16 vaccine (Merck): 8.5 years

- Vaccine. 2009 Rowhani-Rahbar et al,
- During 8.5 years, none of the vaccine recipients was infected with HPV-16 or developed HPV-16-related cervical lesions; among placebo recipients, 6 women were found to be infected with HPV-16 (vaccine efficacy [VE]=100%; 95% confidence interval [CI]: 29-100%) 86% of vaccine recipients remained HPV-16 seropositive at 8.5 years of follow-up.
RCT on bivalent vaccine (GSK): 9.4 years
Naud et al, 2014: Abstract
A subset of 437 women from five Brazilian centers participated for a total of 113 months (9.4 years). VE was 95.6% (86.2, 99.1; 3/50 cases in vaccine and placebo groups, respectively) against incident infection, 100% (84·1, 100; 0/21) against 6-month persistent infection (PI); 100% (61·4, 100; 0/10) against 12-month PI; 97·1% (82.5, 99.9; 1/30) against ≥ ASC-US; 95·0% (68.0, 99.9; 1/18) against ≥ LSIL; 100% (45.2, 100; 0/8) against CIN1+; and 100% (-128.1, 100; 0/3) against CIN2+ associated with HPV-16/18. All vaccinees remained seropositive to HPV-16/18.
THE NORDIC LONG-TERM FOLLOW-UP (LTFU) STUDY OF GARDASIL™ IN PREVIOUSLY VACCINATED WOMEN

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Conflict of Interest: The study is funded by Merck. MR and AS are Merck employees.
Background

1. The long-term follow up study is an extension of FUTURE II quadrivalent HPV vaccination trial
   Registry based follow-up, including HPV typing of biobanked biopsies.

Future II LTFU Study

Start of FUTURE II
5,489 participants

FDA amendment to extend study
• timeframe
• scope

End of LTFU

1st interim report 01.03.2009 biannually until 2020

Study Cohorts and Populations Analyzed

Cohort 1:
- ~2700 subjects who received qHPV vaccine at the start of FUTURE II
- Will contribute approximately 14 years of follow-up after vaccination

Cohort 2:
- ~2100 subjects who received placebo at the start of FUTURE II
- Vaccinated with qHPV vaccine prior to entry into the LTFU study
- Will contribute 10 years of follow-up after vaccination

HNRT
- Received at least 1 vaccination
- Sero-negative and PCR-negative at Day 1 to the appropriate HPV types
- Had any follow-up visit after 1 month following the first injection
- Cases counted following Day 30

Effectiveness of qHPV Vaccine Against HPV 6/11/16/18–Related CIN and Vulvar/Vaginal Cancer

- Sufficient follow-up time to definitively conclude the qHPV vaccine is effective up to 6 years following vaccination\(^1\)
- Results show a trend of continuing protection up to ~8 years\(^1\)
- Additional follow-up time is needed to develop further statistical conclusions\(^2\)

**Per-protocol analysis\(^1\)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n Cases/N Subjects</th>
<th>Person-Years at Risk</th>
<th>Incidence per 100 Person-Years at Risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18–Related CIN and Vulvar/Vaginal Cancer</td>
<td>0/1,902</td>
<td>5,764.6</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td><strong>By Time Since Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 y</td>
<td>0/1,792</td>
<td>739.6</td>
<td>0.0 (0.0–0.5)</td>
</tr>
<tr>
<td>&gt;4 to 6 y</td>
<td>0/1,893</td>
<td>3,416.0</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>&gt;6 to 8 y</td>
<td>0/1,373</td>
<td>1,585.6</td>
<td>0.0 (0.0–0.2)</td>
</tr>
<tr>
<td>&gt;8 to 10 y</td>
<td>0/155</td>
<td>23.1</td>
<td>0.0 (0.0–16.0)</td>
</tr>
<tr>
<td><strong>By Lesion Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN1+ (including CIN2, CIN3, AIS, and/or cervical cancer)</td>
<td>0/1,760</td>
<td>5,247.9</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>Vulvar or vaginal cancer</td>
<td>0/1,899</td>
<td>5,735.7</td>
<td>0.0 (0.0–0.1)</td>
</tr>
</tbody>
</table>

AIS=adenocarcinoma in situ; CI=confidence interval; CIN=cervical intraepithelial neoplasia; qHPV=quadrivalent human papillomavirus

Incidence of Non–Vaccine Related CIN2+ in the LTFU Study of qHPV Vaccine

- No evidence of HPV type replacement against non–vaccine HPV types in women vaccinated ~8 years previously (Cohort 1)

HNRT population\(^1\,^a\); Follow-up since day 1

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<tr>
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<th>Person-Years at Risk</th>
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</tr>
</thead>
<tbody>
<tr>
<td>HPV-Related CIN2+ for All Types Analyzed(^b)</td>
<td>14/1,916</td>
<td>5,792.7</td>
<td>0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>By HPV Type (CIN2+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 31</td>
<td>3/1,824</td>
<td>5,522.3</td>
<td>0.1 (0.0–0.2)</td>
</tr>
<tr>
<td>HPV 33</td>
<td>2/1,854</td>
<td>5,604.7</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>HPV 35</td>
<td>1/1,903</td>
<td>5,752.7</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>HPV 39</td>
<td>0/1,828</td>
<td>5,518.7</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>HPV 45</td>
<td>0/1,864</td>
<td>5,628.3</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>HPV 51</td>
<td>5/1,743</td>
<td>5,289.4</td>
<td>0.1 (0.0–0.2)</td>
</tr>
<tr>
<td>HPV 52</td>
<td>3/1,794</td>
<td>5,423.3</td>
<td>0.1 (0.0–0.2)</td>
</tr>
<tr>
<td>HPV 56</td>
<td>1/1,743</td>
<td>5,286.0</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>HPV 58</td>
<td>3/1,863</td>
<td>5,642.2</td>
<td>0.1 (0.0–0.2)</td>
</tr>
<tr>
<td>HPV 59</td>
<td>2/1,846</td>
<td>5,584.3</td>
<td>0.0 (0.0–0.1)</td>
</tr>
</tbody>
</table>

\(^a\)HNRT population: received at least 1 vaccination; seronegative and PCR negative at day 1 to the appropriate HPV types; had any follow-up visit after 1 month following the first injection; cases counted following day 30.\(^1\)

\(^b\)HPV types analyzed: 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.\(^1\)

CI=confidence interval; CIN=cervical intraepithelial neoplasia; EVG=early vaccination group; HNRT=HPV-naive to the relevant type; LTFU=long-term follow-up; PCR=polymerase chain reaction; qHPV=quadrivalent human papillomavirus.

Conclusions

• There were no cases at all of vaccine type disease for the first 6 years after vaccination.
• Very few cases of CIN2+ with non-vaccine types- no evidence for type replacement.

1 Dillner J, et al.
FUTURE II in Finland

Rana et al, Int J Cancer 2013. Abstract

1,749 16- to 17-year old Finns participated in FUTURE II. A cluster randomized, population-based reference cohort of 15,744 unvaccinated, originally 18-19 year old Finns was established. Cancer Registry linkage (8 years follow-up): For the HPV6/11/16/18, placebo and the unvaccinated reference cohorts, the CIN3 incidence rates were 0/100,000 (95% confidence interval 0.0-106.5), 87.1/100,000 (95% CI 17.9-254.5) and 93.8/100,000 (95% CI 71.4-121), respectively.
Immunogenicity studies

Following an initial decline of neutralizing antibodies, antibody levels reach a plateau – suggestive of very long immunity.

Caveats: Correlate of immunity not (well) established. Antibody assays used did not conform to the international standardisation.
Using cervical cancer incidences to explore whether natural HPV immunity exists

Mathematical models built using a) HPV16 prevalences b) sexual behaviour data c) screening data and d) cervical cancer incidences for Sweden.

Three models: SIS, SIR and waning immunity lasting 5 years.

Waning immunity lasting 5 years gave best fit to data.
Summary

Although conclusive evidence of long-term protection will probably never be obtained, all the data obtained is consistent with very long-term protection.

For practical purposes, consideration of a possible booster vaccination will only be needed in case there would, on very long term follow-up, be increases in incidence of HPV-associated diseases among vaccinees.